Pulmonary Vasoconstriction: the rationale for current therapies

Patients with PAH have reduced circulating levels of the vasodilator and anti-SMC proliferative agent prostacyclin relative to the vasoconstrictor and pro-SMC proliferative compound, thromboxane (S1). This observation led to the institution of continuous i.v. prostacyclin as a therapy, which has often reduced pulmonary vascular resistance, and appreciably improved the quality of life and survival of PAH patients (S2). However, a recent meta-analysis questioned the survival benefit of this and other therapies for PAH (S3).

Experimental studies in rats with hypoxia-induced pulmonary hypertension (S4) coupled with clinical studies documenting increased expression of endothelin in the lungs of patients with PAH (S5), suggested that this powerful vasoconstrictor that promotes SMC proliferation and inflammation may be an important therapeutic target. There are two endothelin receptor subtypes, ET_A and ET_B. These receptors are found in SMCs of blood vessels and both can mediate vasoconstriction, but ET_B receptors on ECs may mediate vasodilatation and endothelin clearance particularly in microvessels (S6). Clinical trials with both the dual endothelin receptor antagonist (S7), as well as with a more selective ET_A receptor antagonist (S8), show alleviation of symptoms and slowing in the progression of disease in some patients. The reduced expression of eNOS (S9) suggested that treatment with phosphodiesterase V inhibitors such as sildenafil to prolong the NO-mediated increase in cGMP, would be effective in dilating PAs (S10) in IPAH as well as in PAH associated with other conditions. Direct comparison of sildenafil with a dual ET receptor antagonist showed comparable results of the two therapies (S11). While one study reported that sildenafil can improve outcome in patients refractory to intravenous prostacyclin (S12), there is no evidence thus far that the orally administered agents can improve upon long-term results with i.v. prostacyclin. New studies related to activation of soluble guanylate cyclase suggest that this approach might be a better strategy (S13). Vasodilator therapies are often used in combination with anticoagulants. Calcium channel blockers are used only in those patients that show a beneficial acute lowering of pulmonary artery pressure and resistance.

Experimental studies have also tried other vasodilators such as adrenomedullin (S14) and vasoactive intestinal peptide (S15). The idea that dropping the level of pulmonary artery pressure may in and of itself reverse even severe PAH is based upon both experimental and

clinical studies. For example, our group showed that transplantation of a rat lung in which monocrotaline had induced severe pulmonary vascular disease into a normal rat was sufficient to reverse lung structural abnormalities (S16). Regression of severe pulmonary vascular disease has been noted to occur in the original lung from a PAH patient that remained after single lung transplant (S17). However, the regression may have been induced by immunosuppressive agents such as rapamycin since these agents can attenuate experimental pulmonary hypertension (S18). The concept of inducing major cytoskeletal changes to drop PA pressure has been recently shown experimentally using the rho kinase inhibitor fasudil (S19); this agent has shown some benefit in acute testing of PAH patients if given by inhalation route to avoid systemic hypotension (S20).

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